Biomaterials Science

# A Polymer Network Architecture Provides Superior Cushioning and Lubrication of Soft Tissue Compared to a Linear Architecture



| | |
|---|---|
| Journal: | *Biomaterials Science* |
| Manuscript ID | BM-COM-05-2023-000753.R1 |
| Article Type: | Communication |
| Date Submitted by the Author: | 16-Sep-2023 |





| | |
|---|---|
| Complete List of Authors: | Cooper, Benjamin; Boston University, Dept of Biomedical Engineering + Chemistry<br>DeMoya, Christian; Boston University, Dept of Biomedical Engineering + Chemistry<br>Sikes, Katie; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>Frisbie, David; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>Phillips, Nikki; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>Nelson, Brad; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>McIlwraith, C.; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>Kawcak, Chris; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>Goodrich, Laurie; Colorado State University College of Veterinary Medicine and Biomedical Sciences<br>Snyder, Brian; Children's Hospital Medical Center<br>Grinstaff, Mark; Boston University, Dept of Biomedical Engineering + Chemistry |
| | |

COMMUNICATION

# A Polymer Network Architecture Provides Superior Cushioning and Lubrication of Soft Tissue Compared to a Linear Architecture

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Benjamin G. Cooper,‡[a, b] Christian D. DeMoya, ‡[b, c] Katie J. Sikes,[d] David D Frisbie, [d] Nikki Phillips, [d] Brad B. Nelson, [d] C. Wayne McIlwraith, [d] Chris E. Kawcak, [d] Laurie R. Goodrich, [d]* Brian D. Snyder,*[b, e] and Mark W. Grinstaff *[a, c]

**We report the relationships between linear vs network polymer architecture and biomechanical outcomes including lubrication and cushioning when the polymers are applied to the surface of articulating knee cartilage. Aqueous formulations of the bioinspired polymer poly(2-methacryloyloxylethyl phosphorylcholine) (pMPC) exhibit tuneable rheological properties, with network pMPC exhibiting increased elasticity and viscosity compared to linear pMPC. Application of a polymer network, compared to a linear one, to articulating tissue surfaces reduces friction, lessens tissue strain, minimizes wear, and protects tissue – thereby improving overall tissue performance. Adminstration of the network pMPC to the middle carpal joint of skeletally mature horses elecits a safe response similar to saline as monitored over a 70 day period.**

## 1. Introduction

Efficient lubrication between articulating tissues is essential for optimal physiological function. Sliding contact against mucosal membranes such as the eyelid, mouth, or intestine, and between articular cartilage surfaces in the joints, is mediated by solutions of macromolecules, macromolecular assemblies, and high-molecular weight biopolymers.[1-3] Examples of natural biolubricants include bottle-brush-structured proteins (mucins),[4] glycoproteins (lubricin),[5, 6] assemblies of phospholipids,[7] and polysaccharides (hyaluronic acid)[8] (Fig. 1a). Shear forces are dissipated by these biolubricants at the site of articulation, reducing tissue wear.

However, as a result of disease, injury, or decades of gradual tissue or biolubricant breakdown, tissue lubrication deteriorates and causes suboptimal or even painful outcomes, such as dry eye and osteoarthritis. Such cases are ordinarily treated by replenishing naturally occurring biolubricants.[9] Viscosupplementation - the intraarticular injection of hyaluronic acid – is one solution but it is no longer the

**New concepts**

Bioinspired materials and functions are advancing our basic knowledge and providing key insights into the use of new technologies for varied applications across commercial sectors. Taking inspiration from natural biolubricants present in the knee joint for proper function, we synthesized zwitterionic linear and network poly(2-methacryloyloxylethyl phosphorylcholine)s (pMPCs) to assess the role and importance of polymer architecture on lubrication of soft deformable materials, like articular tissue. In fact, the dependence of polymer architecture on tissue lubrication performance is unknown, unlike with conventional hard surfaces – yet with potentially significant clinical implications given that more than 100M individuals world-wide suffer from osteoarthritis. Aqueous solutions of pMPC possess tunable storage and loss moduli as well as viscosity over a range of physiologically relevant values, with the network pMPC exhibiting increased elasticity and viscosity at greater polymer concentrations. In two ex vivo 10,000-cycle cartilage-on-cartilage wear tissue experiments of side-by-side and sequential comparison between pMPC and saline, pMPC lowers COF and cushions cartilage by reducing compressive creep strain, thereby protecting cartilage. Moreover, network pMPC, opposed to linear pMPC, demonstrates superior cartilage cushioning, as well as near complete recovery of low COF and ε during sequential pMPC→saline→pMPC testing. Network pMPC is easily administered via a small gauge needle and is a promising lubricant for tissue surfaces.

[a.] *Department of Chemistry, Boston University, Boston, MA, 02215, USA. Email: mgrin@bu.edu*
[b.] *Center for Advanced Orthopedic Studies (CAOS), Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA.*
[c.] *Department of Biomedical Engineering, Boston University, Boston, MA, 02215, USA.*
[d.] *[1]Gail Holmes Equine Orthopaedic Research Center, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, 80523*
[e.] *Department of Orthopedic Surgery, Boston Childrens Hospital, Boston, MA, 02215, USA. Email: Brian.Snyder@childrens.harvard.edu*
‡ These authors contributed equally to this work.
† Electronic Supplementary Information (ESI) available: See
DOI: 10.1039/x0xx00000x

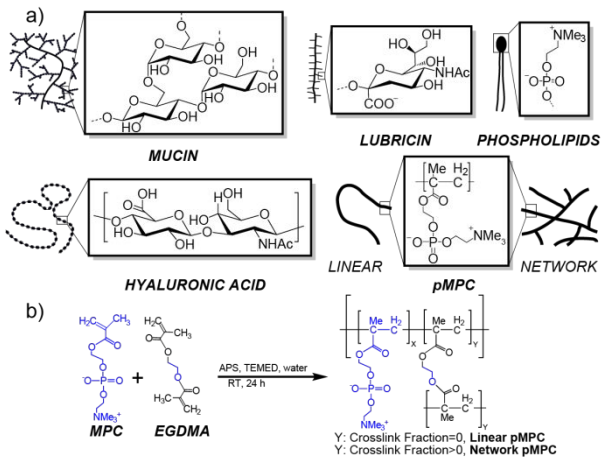


**Fig. 1** (a) Schematic representations of biolubricant macromolecules with variable architectures, which pMPC recapitulates. (b) Synthetic route to linear and network pMPC.

recommended treatment for osteoarthritis, since it has never been shown to significantly prevent or reduce cartilage wear.[10] Several types of cartilage lubricants are being investigated pre-clinically[9] including lubricin[11, 12] and lubricin mimics,[13-15] liposomes,[16] phospholipid coated silk microspheres,[17] synthetic polymer analogues of hyaluronic acid,[18-20] among others.[21-24] Given that endogenous biolubricants span linear, lightly cross-linked, and heavily crosslinked structures (Fig. 1a), we posited that variations in polymer architecture of synthetic polymers will influence lubrication of soft tissues—a known phenomenon with non-deformable hard surfaces,[25] but an unanswered basic science question with potentially significant clinical implications.

Inspired by the structures and compositions of mucins, lubricin, phospholipids, and hyaluronic acid, we identified poly(2-methacryloyloxyethyl phosphorylcholine) (**pMPC**) as it embodies similar hydrophilic character with the coordination of multiple water molecules per repeat unit. The zwitterionic nature of pMPC has been leveraged to form antifouling surfaces, low friction materials, and, more recently, tribosupplements; specifically as the hydrophilic portion of nanoparticles, and multi-block polymers and in combination with linear hyaluronic acid, and polydopamine derivatives.[26-36] To determine the difference in friction-altering capacity between linear and network pMPC, we performed stress-controlled rheometry on apposed *ex vivo* articular cartilage tissues in the presence of various polymer lubricants. Specifically, we report the rheological and lubricating properties of the biolubricants and their performance in an extended, 10,000-cycle wear procedure. Metrics of coefficient of friction and compressive strain, reflecting key attributes of lubrication and cushioning, respectively, are determined and compared between the linear and network polymers documenting the superior performance of the network architecture. Additionally, we describe the results from a pilot large animal safety study after intraarticular administration.

## 2. Results and discussion

### 2.1 Synthesis and characterization of a library of polymeric lubricants

We synthesized linear pMPC at four concentrations of 2-methacryloyloxyethyl phosphorylcholine (MPC) (2, 5, 8, or 12 w/v%; initiator concentration kept constant) via free radical polymerization. We prepared the network architecture similarly via copolymerization with the crosslinker ethylene glycol dimethacrylate (EGDMA) maintained at 1 mol% (mol/mol MPC) (Fig. 1b). Polymers were purified via dialysis, lyophilized, and resuspended in deionized water at the corresponding concentration of initial reactions. We measured the molecular weight ($M_W$) of the linear polymers via gel permeation chromatography (GPC) (Table 1; SI Fig. S1). For the network polymers, which have an infinite $M_W$, we hydrolyzed the polymers with sodium hydroxide to determine the $M_W$ of the linear portion of the network architectures by GPC (Table 1; Fig. 2a; SI Fig. S1). We obtained polymers in high yield (>80%) and higher than expected $M_W$. As expected, not all of the initiator in the APS polymerization initiates giving higher $M_W$s. Recent advances in RAFT polymerization of MPC highlight excellent

**Table 1** Molecular weights of linear polymers and of linear portions of network polymers, and crosslink fraction of network polymers.

| Polymer Concentration | Linear $M_W$ (MDa), PDI | Hydrolyzed Network $M_W$ (MDa), PDI | Crosslink Fraction of Network |
|---|---|---|---|
| 2 w/v% | 0.55, 1.45 | 0.28, 1.37 | 0.11 |
| 5 w/v% | 0.61, 1.88 | 0.74, 1.20 | 0.10 |
| 8 w/v% | 0.87, 3.16 | 1.20, 1.25 | 0.13 |
| 12 w/v% | 1.58, 3.46 | 1.16, 1.32 | 0.14 |

control over Mw and dispersity,[32] and overcome this limitation. The $M_W$ increases for both linear and network polymers with increasing polymer concentration. For the network polymer, we kept the crosslinker to monomer ratio constant and as such the crosslinking fraction stays constant. After hydrolysis of the network, the viscosity of the polymer solution decreases and is similar to the viscosity of linear pMPC, demonstrating effective breaking of the crosslinks, while NMR data confirm the presence of the phosphorylcholine group following hydrolysis (SI Fig. S2 and S3).

For rheometry, we first performed an oscillatory stress sweep at 2.5 Hz to obtain the storage (G') and loss (G") moduli in the lubricant's linear viscoelastic region (Fig. 2b; SI Fig. S4). G" are similar for network and linear pMPC at 2 and 5 w/v%; however, at increased concentrations, the G" of the network polymer is significantly greater than the linear counterparts. The greater viscous nature of network relative to linear polymers is consistent with a branched network's increased steric chain confinement.[37] Increasing the concentration of the polymer network affords a higher viscosity solution (Fig. 2C). The increased viscosity is due to the additional polymer present in solution at 12 w/v% compared to 8 w/v%, as diluting the 12

 

w/v% formulation to an 8 w/v% formulation affords a viscosity similar to the as prepared 8 w/v% formulation (Fig. S5). G' are invariant with MPC concentration at lower concentrations (2, 5, and 8 w/v% formulations), but the 12 w/v% lubricant (particularly network architecture) exhibits a marked increase in G', explained by the existence of a minimum polymer concentration necessary for sufficient interaction among polymer chains to cause the cessation of purely viscous behavior and the appearance of weak elasticity.[38] The phase angles (δ) for the four lubricants of varying MPC concentration agree with this phenomenon; for the 2, 5, and 8 w/v% formulations, increased viscosity without elastic character causes an increase in δ, but δ decreases for the 12 w/v% formulation owing to its elasticity arising from surpassing the polymer concentration critical for elastic inter-chain interactions (SI Fig. S6). Further, the crossover frequencies for each lubricant (i.e., when G'=G") positively correlate with lubricant concentration (SI Fig. S7). pMPC viscosities span approximately three orders of magnitude as determined via a continuous flow shear rate sweep experiment, with a positive correlation between polymer concentration and viscosity (Fig. 2c). Network polymers at 8 and 12 w/v% exhibit higher viscosities than concentration-matched linear polymers (Fig. 2c).

Next, we measured the crosslink fraction, defined as the number of crosslinking units per MPC units in a single polymer chain, of the network architectures. We used a fluorescent crosslinker, succinic acid-bisphenol A glycerolate dimethacrylate (SA-BAGDMA), as a model crosslinker to measure the crosslink fraction of the network pMPC. We copolymerized MPC with SA-BAGDMA at the same concentration as EGDMA for the 2, 5, 8 and 12 w/v% EGDMA formulations (Fig. 2d). We confirmed that SA-BAGDMA incorporates into the pMPC network at a similar concentration to EGDMA by comparing the average viscosity of each lubricant between shear rates of 10 and 100 $s^{-1}$. The average viscosities of network pMPC prepared with SA-BAGDMA are not significantly different from concentration matched network pMPC prepared with EGDMA (Fig. 2e). Also, the slightly increased viscosity of the 2 or 5 w/v% linear pMPC compared to 2 or 5 w/v% network pMPC made with EGDMA or SA-BAGDMA is non-significant ($p > 0.99$ for EGDMA and SA-BAGDMA.) The network SA-BAGDMA based pMPC average viscosity increases with increasing polymer concentration, analogous to the EGDMA based formulations, consistent with the two crosslinkers performing similarly. The crosslink fraction, as determined by fluorescence, does not vary significantly across polymer concentrations, indicating that crosslinker incorporation into pMPC is independent of polymer concentration (Table 1). A crosslink fraction of 0.14 for the 12 w/v% network pMPC reflects that the network architecture is the main component that leads to the increased viscosity, G', and G" compared to the linear counterpart, and that the network architecture impacts the rheological properties of pMPC at high concentrations. As a further control, the G' and G'' for solutions of non-polymerized MPC monomer ranging in concentration from 2 to 12 w/v%, are similar to those of

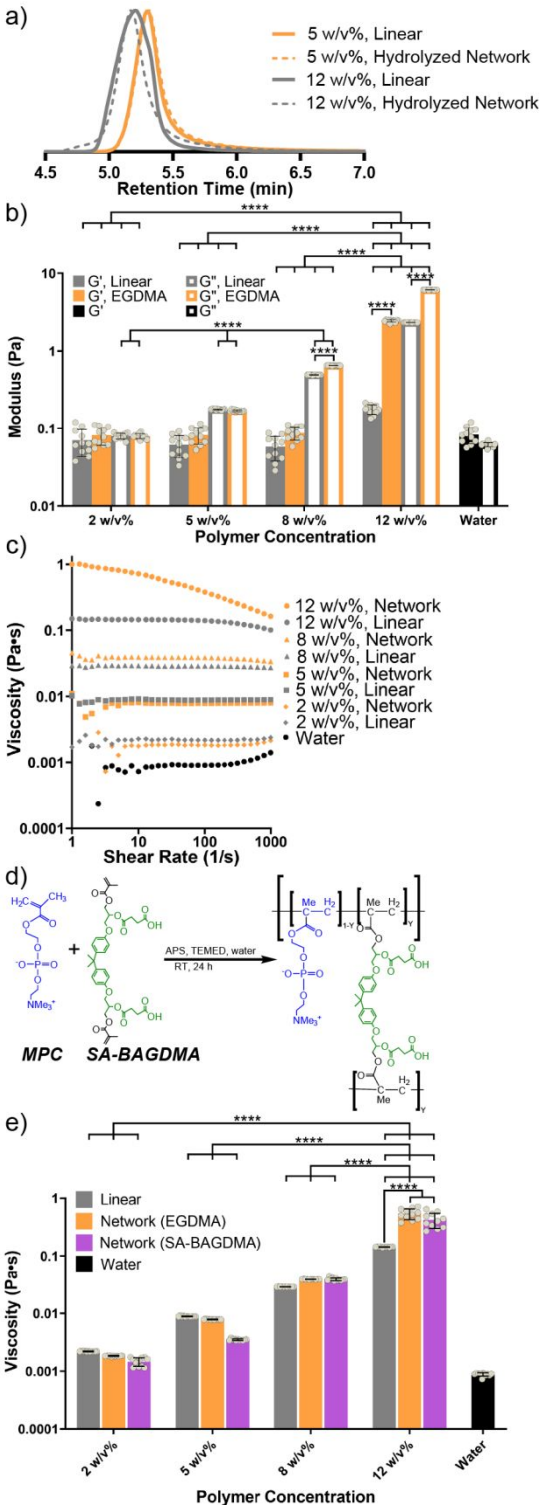


**Fig. 2** (a) Storage and loss moduli for linear and network pMPC at varying concentrations. Moduli averaged over 11 logarithmically-spaced data points spanning stress 1-10 Pa; error bars, standard deviations. N=3 (b) Viscosity as a function of shear rate. (c) GPC traces of linear and linear portion of network pMPC (Hydrolyzed Network) at 5 w/v% and 12 w/v%. (d) Synthetic route of network pMPC with the fluorescent crosslinker, SA-BAGDMA. (e) Viscosity of the pMPC library, averaged across 11 logarithmically-spaced data points spanning 10-100 $s^{-1}$. **** = $p<0.0001$. Significance bars across concentrations refer to polymer architecture and measurement (i.e., G' or G") matched samples.

deionized water, indicating that the lubricant rheological properties are not determined by solute mass alone, but rather by inherent polymer viscosity and inter-chain viscous interactions (SI Fig. S8).

**2.2 Functional assessment of pMPC lubrication and cushioning of *ex vivo* cartilage** Following rheological characterization, we assessed the friction lowering capacity of linear and network pMPC in comparison to saline over the duration of a simultaneous compressive creep and torsional disc-on-disc friction test. We investigated a pMPC concentration of 5 w/v%, as greater concentrations did not easily pass through a 25-gauge syringe—an optimal design requirement for therapeutic use via intra articular injection. As a model tissue, bovine osteochondral cylindrical explants ("plugs," Ø 7 mm) were aligned collinearly with mated cartilage surfaces in contact, and 10,080 rotations were applied under a constant compressive stress (0.78 MPa) with plugs submerged in either saline, linear, or network pMPC, having been incubated in lubricant for the prior 18 h, N=3-4 each group. From the collected torque, force, and displacement data, we calculated the coefficient of friction (COF) and creep deformation normalized by initial cartilage thickness (i.e., engineering compressive strain, ε). The saline group's COF increases over time, reaching an average value over the final one third of the test's duration ($COF_{eq}$) of 0.0363 ± 0.0079 (Fig. 3a). The linear pMPC group's $COF_{eq}$ is 0.0089 ± 0.0013, while that of the network pMPC group is 0.0097 ± 0.0054, or 75 and 73% less, respectively, than that of saline. Linear and network pMPC COFs are statistically significantly ($p < 0.05$) less than that of saline for all points beyond the first 1600 seconds of the test, but are not statistically significantly different from each other. We attribute pMPC's friction reduction to the lubricant's ability to dissipate shear forces at the cartilage-cartilage interface. The origins of this force dissipation are two-fold: first, the polymer's pendant phosphorylcholine groups immobilize numerous water molecules while being compressed, yet exhibit a fluidity of motion of water molecules under shear, transitioning the articulation slip-plane away from the tissue surface and towards the zwitterionic moieties, thus lowering COF;[39, 40] second, the solution of pMPC allows for translation of the shear forces of articulation into entropic dissipation of energy through the polymer's flexible backbone.[41]

The tissue's compressive strain, ε, also increases over time, reaching an equilibrium ($\varepsilon_{eq}$) at 40 ± 8% compression for the group lubricated by saline, while linear pMPC's $\varepsilon_{eq}$ is 34 ± 7% ($p = 0.35$ vs saline) and network pMPC's $\varepsilon_{eq}$ is 23 ± 7% ($p = 0.049$ vs saline) (14 and 43% lesser than saline, respectively) (Fig. 3b). Tissue cushioning (i.e., attenuation of $\varepsilon_{eq}$) occurs through two potential mechanisms: 1) polymer penetration into tissue fills pores within the matrix and therefore increases its compressive stiffness, and/or 2) the polymer's ability to reduce tissue frictional shear forces mitigates compressive deformation.[42] For the former explanation to be operative, time is required for polymer penetration into the tissue, whereas a simple exogenous lubricant that does not penetrate the tissue would reduce friction immediately (provided it does not require time to adhere to its substrate). To investigate this distinction, we repeated the torsional creep test on a group of plug pairs that were introduced to pMPC immediately upon the test's beginning. The network pMPC's frictional and creep properties are similar whether it was introduced immediately to or incubated overnight with the cartilage, rendering pMPC

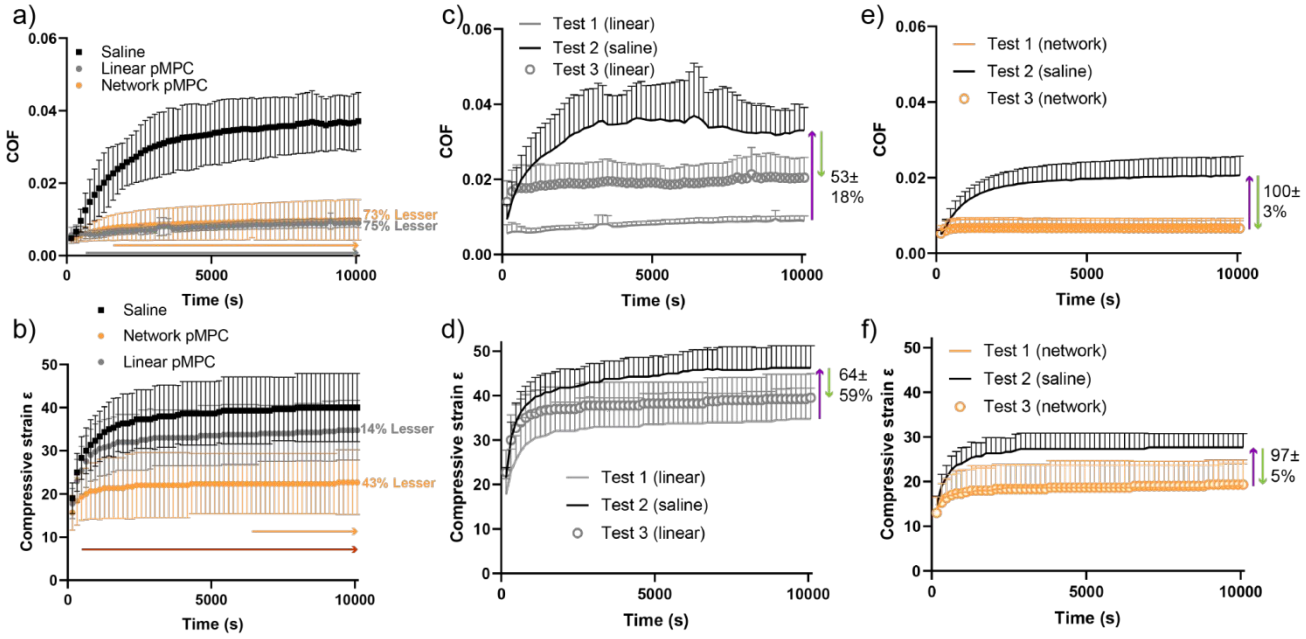


**Fig. 3** COF (a) and ε (b) versus time over the course of a simultaneous creep and torsional articulation test for groups of plug pairs lubricated by either saline, linear pMPC, or network pMPC. Arrows indicate periods of statistically significant differences ($p<0.05$) in COF and compressive strain (grey, comparing linear pMPC with saline; orange, comparing network pMPC with saline; red, comparing linear with network pMPC). COF (c, e) and ε (d, f) as a function of time for friction tests on three successive days (Tests 1-3) under lubrication by pMPC, saline, then pMPC again; conducted separately with linear (c, d) and network (e, f) pMPC. Arrows indicate fold increase Test 1→2 and decrease Test 2→3 (magenta and green, respectively). Average $COF_{eq}$ and $\varepsilon_{eq}$ recovery, right of green arrow. N=3-4

 

penetration into the tissue unnecessary. Consistent with this result, FTIR spectroscopy of cartilage incubated overnight in network pMPC shows no presence of pMPC within the matrix. In fact, one of the rationales for selecting a network polymer is its large molecule weight to increase joint residence time. The molecular weight cutoff of the synovial membrane is ~750 kDa for proteins, and ~200 kDa for synthetic polymers.[43, 44] Additionally, pMPC is not susceptible to degradation by hyaluronidase, which will extend its joint residency time (Fig. S9).

In contrast to the linear and network pMPC lubricants exhibiting similar COF decreases, the network pMPC formulation affords superior cushioning (statistically significant difference in ε values, Fig. 3b). We hypothesized that the difference in ε attenuation arises from the network lubricant's locally-increased viscosity while compressed between apposing tissue surfaces. This "boosted" lubrication phenomenon[45, 46] manifests as a gel-like, water-retarding polymer layer between the articulating surfaces, thus reducing the tissue deformation as water molecules are sterically hindered from exuding from the tissue; in contrast, the linear polymers do not form such gel layer upon compression, hence, water's expulsion from the tissue is not reduced, increasing creep deformation. The ability to attenuate compressive strain serves the important biological function of cushioning tissue upon loading, as articulation under high strains correlates with increased wear.[45]

### 2.3 Simulation of pMPC performance upon re-administration to an articulating surface

In a second experiment, we performed an identical friction procedure on three successive days on a single group of plug pairs (n=3-4), under lubrication by pMPC (linear or network), then by saline the following day, and finally by the same pMPC formulation once again on the third day. The purpose of this pMPC→saline→pMPC lubrication sequence is to assess the robustness of repeated lubricant exposure as a potential injectable therapy and to investigate mechanism of action as a lubricant that does not permanently alter the tissue. Prior to each test, plug pairs were incubated for 18 hours at 4 °C, and we performed tests with plugs submerged in the appropriate lubricant. After each test, plugs re-swell to equilibrium in saline for 3 hours with moderate shaking. In this experiment, each sample group experiences an initially low $COF_{eq}$ during Test 1, followed by an increase in $COF_{eq}$ during Test 2, and finally a partial or full "recovery" of $COF_{eq}$ during Test 3 (Fig. 3c, e). The average recovery of $COF_{eq}$ (given by the average quotient of the fold increase Test 1 to 2 divided by fold decrease Test 2 to 3) is 53 ± 18% for linear pMPC and 100 ± 3% for network pMPC (averages statistically significantly different). Similarly, percent recovery of $\varepsilon_{eq}$ is 64 ± 59% for linear pMPC and 97 ± 5% for network pMPC (no statistical difference) (Fig. 3d, f).

Thus, the network pMPC exhibits near complete recovery of both $COF_{eq}$ and $\varepsilon_{eq}$, which leads to several conclusions. First, despite the relatively large standard deviations (SD) on the fold increase and fold decrease in $COF_{eq}$ between subsequent tests (relative SD 45 and 38%, respectively), the near 100% average recovery of $COF_{eq}$ and its low SD (relative SD 3%) indicates that network pMPC functions remarkably similarly even for biological specimens that have inherent variability in natural frictional properties. This property lends promise to the potential utility of network pMPC as a therapeutic agent for individuals with varying cartilage material properties. In contrast, use of linear pMPC only provides partial recovery, likely due to the occurrence of mild wear (surface roughening causing increased COF and tissue softening causing increased ε). Second, the recovery of $COF_{eq}$ and especially of $\varepsilon_{eq}$ upon lubrication by network pMPC indicates that pMPC ostensibly does not have long-term effects that compound upon multiple friction tests, i.e., by demonstrating that friction and creep deformation increase when pMPC is removed but then are restored to nearly identical levels following its reintroduction. Thus, the network pMPC's mechanism of action is as a lubricant which does not permanently alter tissue mechanical properties even after it has been removed.

### 2.4 Pilot safety data in an equine model.

Finally, we assessed the safety of pMPC *in vitro* and *in vivo*. The 5 w/v% linear and network polymer are non-cytotoxic to chondrocytes and fibroblasts (NIH-3T3s) at all concentrations studied, while the viability of synoviocytes begins to decrease at high concentrations - 50 mg/mL, indicating that synoviocytes are more susceptible to pMPC cytotoxicity than chondrocytes and fibroblasts (SI fig. S10). We then performed a pilot equine study to assess acute safety, and administered the 5 w/v% network pMPC or saline into the middle carpal joint of skeletally mature horses (N=8). We monitored the horses for 70 days post injection, and collected the synovial fluid and scored the joint

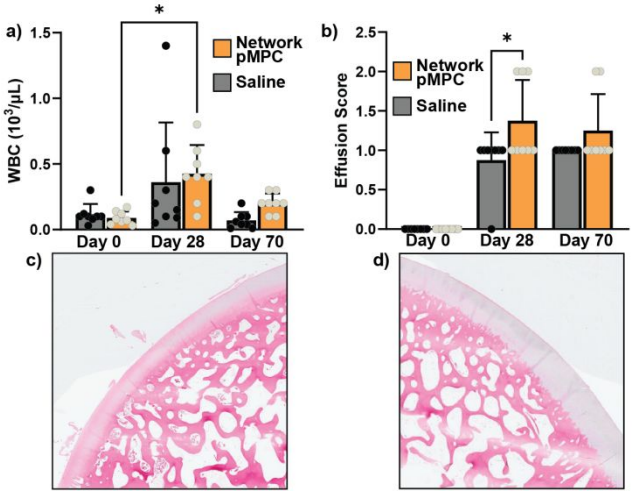


**Fig. 4** Pilot safety study of network pMPC after intraarticular administration of network pMPC in the middle carpal joint of skeletally mature horses. (a) White blood cell (WBC) count from collected synovial fluid for the saline and network pMPC treatment groups. (b) Joint effusion score for the saline and network pMPC treatment groups. (C and D) H&E staining of cartilage at 70 days after intraarticular administration of saline or network pMPC, respectively. * = $p<0.05$.

effusion on a scale of 1 to 4 at days 0, 28, and 70. The total white blood cell (WBC) count increases in both the pMPC and saline treatment groups from day 0 to 28 ($p < 0.05$), and then subsequently subsides at day 70 (Fig. 4A). Similarly, the effusion score significantly increases for both pMPC and saline treatment groups from day 0 to day 28, with a greater response from pMPC ($p < 0.5$). The difference between the two groups subsides to a non-significant difference at day 70 (Fig. 4b). Following euthanasia, the cartilage from each carpus was harvested, sectioned, and stained with hematoxylin and eosin (H&E; Fig. 4c and d). H&E staining shows no distinguishable differences between joints injected with pMPC or saline, as both treatments result in intact, full thickness cartilage. These pilot safety data support further *in vivo* evaluation of pMPC.

## 3. Conclusions

In conclusion, aqueous solutions of the bioinspired synthetic polymer pMPC augment the frictional and compressive properties of bovine articular cartilage during multiaxial mechanical testing. Lubricant solutions possess tunable storage and loss moduli as well as viscosity over a range of physiologically relevant values, with the network pMPC exhibiting increased elasticity and viscosity at greater concentrations. In two *ex vivo* cartilage-on-cartilage tissue experiments of side-by-side and sequential comparison between pMPC and saline, pMPC lowers COF and cushions by reducing compressive creep strain, thereby protecting cartilage. Moreover, network pMPC opposed to linear pMPC demonstrates superior cushioning, as well as near complete recovery of low COF and ε during sequential pMPC→saline→pMPC testing. This study reveals the capacity of an exogenous lubricant to improve not only frictional response but also compressive response of the tissue, indicating a wider potential therapeutic utility of such synthetic biolubricants in the treatment of articulating tissue diseases such as osteoarthritis. pMPC based lubricants overcome several shortcomings of HA based viscosupplements, namely they are: 1) chemically synthesized and of a known composition; 2) injectable through a small 25G needle thereby inflicting less pain; 3) sterilizable (SI Fig. S11); 4) chondroprotective in an ex vivo cartilage-on-cartilage plug model; and 5) not susceptible to degradation by hyaluronidase. Importantly the conclusions from this study provide key insights and requirements for the design of optimal tissue synthetic biolubricants—as it is likely that various tissue surfaces will need a unique polymer architecture (i.e., nonlinear) —and thus significant opportunities exist for the synthesis and tribological characterization of new polymer compositions, structures, and architectures.

## Author Contributions

B. G. C, C. D. D., and M. W. G. conceptualized and designed the experiments. B. G. C, and C. D. D. conducted experiments. B. G. C, C. D. D., B. D. S., and M. W. G. interpreted data, drafted the manuscript, and provided meaningful comments and edits.

## Conflicts of interest

A patent was filed by the university on the polymers and is available for licensing. No IP has been licensed to the authors.

## Acknowledgements

The authors gratefully acknowledge Boston University, the Harvard Catalyst Foundation, the Wallace H. Coulter Foundation, and the National Science Foundation Graduate Research Fellowship Program (DGE-1247312 B.G.C., DGE-1840990 C.D.D.), and Ms. Shikha Sharma and Dr. Stacy Chin for assistance with the cell studies.

### Author contributions

Conceptualization: BC, CDM, BDS, MWG
Methodology: BC, CDM, KJS, DDF, NP, BBN, CEK, LRG
Investigation: BC, CDM, KJS, DDF, NP, BBN, LRG
Visualization: BC, CDM, NP,
Supervision: CWM, CEK, LRG, BDS, MWG
Writing—original draft: BC, CDM,
Writing—review & editing: All authors
Funding: MWG



| | ORCID | email |
|---|---|---|
| Benjamin Copper | 0000-0002-5477-9051 | bgcooper515@gmail.com |
| Christian DeMoya | 0000-0001-6869-6188 | cdemoya@bu.edu |
| Katie J. Sikes | | katie.sikes@colostate.edu |
| David D Frisbie | | david.frisbie@colostate.edu |
| Nikki Phillips | | Jennifer.Phillips@colostate.edu |
| Brad B. Nelson | | Brad.Nelson@colostate.edu |
| C. Wayne McIlwraith | | Wayne.McIlwraith@colostate.edu |
| Chris E. Kawcak | | ckawcak@colostate.edu |
| Laurie R. Goodrich | | Laurie.Goodrich@ColoState.edu |
| Brian D. Snyder | | Brian.Snyder@childrens.harvard.edu |
| Mark Grinstaff | 0000-0002-5453-3668 | mgrin@bu.edu |



References

1. Z. M. Jin, M. Stone, E. Ingham and J. Fisher, *Current Orthopaedics*, 2006, **20**, 32-40.

 

2. A. Dedinaite, *Soft Matter*, 2012, **8**, 273-284.
3. D. Dowson and A. Neville, *Proceedings of the Institution of Mechanical Engineers Part J-Journal of Engineering Tribology*, 2006, **220**, 109-123.
4. J. M. Coles, D. P. Chang and S. Zauscher, *Current Opinion in Colloid & Interface Science*, 2010, **15**, 406-416.
5. D. H. Veeregowda, H. C. van der Mei, J. de Vries, M. W. Rutland, J. J. Valle-Delgado, P. K. Sharma and H. J. Busscher, *Clinical Oral Investigations*, 2012, **16**, 1499-1506.
6. B. Zappone, M. Ruths, G. W. Greene, G. D. Jay and J. N. Israelachvili, *Biophysical Journal*, 2007, **92**, 1693–1708.
7. B. A. Hills, *Journal of Rheumatology*, 1989, **16**, 82-91.
8. V. C. Mow and R. Huiskes, *Basic Orthopedic Biomechanics and Mechanobiology*, Lippincott Williams & Wilkins, Philadelphia, 3rd edn., 2005.
9. B. G. Cooper, C. Bordeianu, A. Nazarian, B. D. Snyder and M. W. Grinstaff, *Biomaterials*, 2018, **181**, 210-226.
10. D. S. Jevsevar, *Journal of the American Academy of Orthopaedic Surgeons*, 2013, **21**, 571-576.
11. K. A. Waller, K. E. Chin, G. D. Jay, L. X. Zhang, E. Teeple, S. McAllister, G. J. Badger, T. A. Schmidt and B. C. Fleming, *American Journal of Sports Medicine*, 2017, **45**, 1512-1521.
12. C. R. Flannery, R. Zollner, C. Corcoran, A. R. Jones, A. Root, M. A. Rivera-Bermudez, T. Blanchet, J. P. Gleghorn, L. J. Bonassar, A. M. Bendele, E. A. Morris and S. S. Glasson, *Arthritis and Rheumatism*, 2009, **60**, 840-847.
13. A. Lawrence, X. Xu, M. D. Bible, S. Calve, C. P. Neu and A. Panitch, *Biomaterials*, 2015, **73**, 42-50.
14. K. J. Samaroo, M. Tan, D. Putnam and L. J. Bonassar, *Journal of Orthopaedic Research*, 2017, **35**, 548-557.
15. I. S. Bayer, *Lubricants*, 2018, **6**, 30.
16. S. Sivan, A. Schroeder, G. Verberne, Y. Merkher, D. Diminsky, A. Priev, A. Maroudas, G. Halperin, D. Nitzan, I. Etsion and Y. Barenholz, *Langmuir*, 2010, **26**, 1107-1116.
17. R. Zheng, J. Zhan, X. Wang, D. Kaplan, N. Pesika and V. T. John, *Particle & Particle Systems Characterization*, 2013, **30**, 133-137.
18. B. A. Lakin, B. G. Cooper, L. Zakaria, D. J. Grasso, M. Wathier, A. M. Bendele, J. D. Freedman, B. D. Snyder and M. W. Grinstaff, *ACS Biomater Sci Eng*, 2019, **5**, 3060-3067.
19. G. Q. Liu, Z. L. Liu, N. Li, X. L. Wang, F. Zhou and W. M. Liu, *Acs Applied Materials & Interfaces*, 2014, **6**, 20452-20463.
20. M. Wathier, B. A. Lakin, B. G. Cooper, P. N. Bansal, A. M. Bendele, V. Entezari, H. Suzuki, B. D. Snyder and M. W. Grinstaff, *Biomaterials*, 2018, **182**, 13-20.
21. G. Morgese, E. Cavalli, J. G. Rosenboom, M. Zenobi-Wong and E. M. Benetti, *Angewandte Chemie-International Edition*, 2018, **57**, 1621-1626.
22. A. Tnibar, H. Schougaard, L. Camitz, J. Rasmussen, M. Koene, W. Jahn and B. Markussen, *Acta Veterinaria Scandinavica*, 2015, **57**, 20.
23. S. Lee, M. Muller, M. Ratoi-Salagean, J. Voros, S. Pasche, S. M. De Paul, H. A. Spikes, M. Textor and N. D. Spencer, *Tribology Letters*, 2003, **15**, 231-239.
24. M. Benz, N. H. Chen and J. Israelachvili, *Journal of Biomedical Materials Research Part A*, 2004, **71A**, 6-15.
25. S. Giasson, J. M. Lagleize, J. Rodriguez-Hernandez and C. Drummond, *Langmuir*, 2013, **29**, 12936-12949.
26. H. Chen, T. Sun, Y. Yan, X. Ji, Y. Sun, X. Zhao, J. Qi, W. Cui, L. Deng and H. Zhang, *Biomaterials*, 2020, **242**, 119931.
27. J. Faivre, B. R. Shrestha, G. Xie, M. Olszewski, V. Adibnia, F. Moldovan, A. Montembault, G. Sudre, T. Delair, L. David, K. Matyjaszewski and X. Banquy, *Chemistry of Materials*, 2018, **30**, 4140-4149.
28. S. Feng, J. Li, X. Li, S. Wen and Y. Liu, *Applied Materials Today*, 2022, **27**, 101499.
29. L. Han, L. Xiang, J. Zhang, J. Chen, J. Liu, B. Yan and H. Zeng, *Langmuir*, 2018, **34**, 11593-11601.
30. Q. Li, C. Wen, J. Yang, X. Zhou, Y. Zhu, J. Zheng, G. Cheng, J. Bai, T. Xu, J. Ji, S. Jiang, L. Zhang and P. Zhang, *Chem Rev*, 2022, **122**, 17073-17154.
31. W. Lin, N. Kampf, R. Goldberg, M. J. Driver and J. Klein, *Langmuir*, 2019, **35**, 6048-6054.
32. R. Xie, H. Yao, A. S. Mao, Y. Zhu, D. Qi, Y. Jia, M. Gao, Y. Chen, L. Wang, D. A. Wang, K. Wang, S. Liu, L. Ren and C. Mao, *Nat Biomed Eng*, 2021, **5**, 1189-1201.
33. L. Yang, L. Sun, H. Zhang, F. Bian and Y. Zhao, *ACS Nano*, 2021, **15**, 20600-20606.
34. Y. Zheng, Y. Yan, W. Zhao, H. Wang, Y. Sun, J. Han and H. Zhang, *ACS Appl Mater Interfaces*, 2022, **14**, 21773-21786.
35. P. E. Milner, M. Parkes, J. L. Puetzer, R. Chapman, M. M. Stevens, P. Cann and J. R. T. Jeffers, *Acta Biomater*, 2018, **65**, 102-111.
36. T. Moro, M. Kyomoto, K. Ishihara, K. Saiga, M. Hashimoto, S. Tanaka, H. Ito, T. Tanaka, H. Oshima, H. Kawaguchi and Y. Takatori, *J Mech Behav Biomed Mater*, 2014, **31**, 100-106.
37. M. Seiler, *Fluid Phase Equilibria*, 2006, **241**, 155-174.
38. C. Michon, G. Cuvelier and B. Launay, *Rheologica Acta*, 1993, **32**, 94-103.
39. A. Gaisinskaya, L. Ma, G. Silbert, R. Sorkin, O. Tairy, R. Goldberg, N. Kampf and J. Klein, *Faraday Discussions*, 2012, **156**, 217-233.
40. L. Ma, A. Gaisinskaya-Kipnis, N. Kampf and J. Klein, *Nature Communications*, 2015, **6**, 6060.
41. J. Klein, E. Kumacheva, D. Mahalu, D. Perahia and L. J. Fetters, *Nature*, 1994, **370**, 634-636.
42. J. Katta, Z. Jin, E. Ingham and J. Fisher, *Osteoarthritis and Cartilage*, 2009, **17**, 662-668.
43. P. A. Simkin and J. E. Bassett, *J Rheumatol*, 2011, **38**, 2635-2642.
44. B. Sterner, M. Harms, S. Woll, M. Weigandt, M. Windbergs and C. M. Lehr, *Eur J Pharm Biopharm*, 2016, **101**, 126-136.
45. H. Forster and J. Fisher, *Proceedings of the Institution of Mechanical Engineers Part H-Journal of Engineering in Medicine*, 1999, **213**, 329-345.